Guest Editorial — William J. Blot [1,2] and Joseph F. Fraumeni, Jr. [1]

Passive Smoking and Lung Cancer [3]

Passive smoking, the inhalation of smoke from tobacco products used by others, was first associated with human cancer in 1981 when two publications reported higher rates of lung cancer among nonsmoking women married to smokers (*1*, *2*). The findings were greeted with some skepticism, in part because of questions raised about the methods used, but mostly because it was thought unlikely that nonsmokers would receive sufficient smoke exposure to more than double their risk of lung cancer as these reports suggested. Considerable evidence has accumulated in the interim, so that a review of the topic now seems timely to summarize where we stand and to help identify new avenues of research on passive smoking and cancer. This review is restricted to lung cancer, since information to assess the potential effect of passive smoking on other cancers is still inadequate. We first comment on the individual epidemiologic studies evaluating passive smoking, then combine data to provide a summary estimate of the RR of lung cancer among nonsmoking women married to smokers. Difficulties in exposure assessment are examined, then taken into account in our assessment of the passive smoking-lung cancer relation.

INITIAL STUDIES

The reports of Hirayama from Japan (*1*) and Trichopolous et al. from Greece (*2*) showing increases in lung cancer risk among nonsmoking women married to smokers were derived from two different types of epidemiologic investigation. The study in Japan used the cohort approach, in which death rates for various diseases were determined among 265,000 persons comprising 95% of the population aged 40–59 in 29 health center districts. For each of these individuals a 1-page questionnaire had been completed in 1965, indicating whether the individual was a cigarette smoker and how many cigarettes per day he or she smoked. For the period 1965–81, 200 lung cancer deaths were recorded among nonsmoking married women, with death rates increasing in proportion to the amount of cigarettes smoked by their husbands in 1965 (*3*, *4*). Table 1 describes the trend, indicating a 90% excess in lung cancer among nonsmoking females whose husbands smoked 20 or more cigarettes per day. No increase in mortality from other cancers, except for nasal and brain tumors, was detected in this group. Among nonmalignant diseases, the excess in death rates for emphysema-chronic bronchitis reached 60% among women married to heavy smokers, with a similar but less steep trend for ischemic heart disease. For no major disease, however, was the association with passive smoking as marked as for lung cancer.

The study in Greece was a hospital-based case-control investigation of lung cancer (*2*, *5*, *6*). Cases were women with lung cancers other than adenocarcinoma admitted to one of the three largest hospitals treating respiratory cancer in Athens, while controls were selected from a single Athens orthopedic hospital. Interviews with the subjects revealed 77 cases and 225 controls who had not smoked cigarettes. Among these nonsmoking women, RRs of lung cancer were higher for those married to smokers than for those married to nonsmokers, long-term ex-smokers, or never married women and tended to increase according to amount smoked by the husband (table 2).

Some criticism of the reports quickly surfaced (*7–10*). Neither study evaluated exposure to environmental tobacco smoke outside the home. A potential statistical error was noted in the Hirayama report, although its impact was negligible (*7–9*). The Hirayama article provided only meager details of the methods used in the conduct and analysis, so some questions were raised about the cohort and its follow-up. Subsequent reports by Hirayama (*3*, *4*, *11*) still omit detailed discussion of study design, but several aspects of the investigation weigh against the possibility that inherent biases account for the elevated risk observed with passive smoking. These include the prospective nature of the study, with information on smoking obtained prior to the follow-up for cancer deaths; the dose-response relation evident via internal comparisons, with death rates for segments of the cohort (nonsmoking women married to light, moderate, or heavy smokers) progressively higher than rates in another segment of the same cohort (nonsmoking women married to nonsmokers); and the completeness of ascertainment of mortality available through the Japanese national system of mortality registration, so that

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ABBREVIATIONS USED: CI = confidence interval; RR = relative risk.

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[3] Received March 28, 1986.

Editor's note: Periodically, the Journal publishes solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors welcomes suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the causes, cure, or prevention of cancer.

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TABLE 1.—*Ratios of lung cancer mortality, 1966–81, among nonsmoking Japanese females according to the smoking habits of their husbands*[a]

Husband's smoking status	No. of lung cancer deaths	Mortality ratios	90% CI
Nonsmoker	37	1.0	—
Ex-smoker	17	1.4	0.9–2.2
1–14 cigarettes/day	58	1.4	1.0–2.0
15–19 cigarettes/day	24	1.5	1.0–2.4
≥20 cigarettes/day	64	1.9	1.3–2.7

[a] Data from (*3*).

virtually all deaths could be identified among the various subgroups of the cohort. Determination of cause of death was not described in the Hirayama publications, and it is suspected that the lung cancers reported for many of the women may have been diagnosed solely on clinical or radiologic evidence. There is no reason to suspect, however, that diagnostic differentials exist according to the smoking status of the husband. Histologic confirmation was also not obtained on all patients in the Greek study, and the cases and controls were derived from different hospitals (although both groups were similar on demographic and socioeconomic grounds). Despite their limitations, the studies of Hirayama and Trichopoulos et al. yielded remarkably consistent results and served to stimulate additional research to evaluate environmental tobacco smoke as a risk factor for cancer.

RECENT EPIDEMIOLOGIC INVESTIGATIONS

Since 1981 several studies in the United States (table 3) and abroad (table 4) have assessed lung cancer risk among persons exposed to environmental tobacco smoke. Few were designed specifically to evaluate passive smoking and thus typically obtained only limited exposure information. In combination, however, they provide some clarification of the patterns of risk among passive smokers.

American Cancer Society Study

The first report subsequent to the Japanese and Greek investigations was based on existing data from the American Cancer Society's cohort mortality study. Garfinkel (*12*) identified 176,000 married women throughout the United States who indicated in a questionnaire administered in 1959 that they had never smoked cigarettes regularly and for whom information on their husband's smoking habits was available. A total of 153 lung cancer deaths were recorded during 1960–72 among this group. Small elevations in lung cancer mortality were found among women married to light (RR = 1.3) or heavy (RR = 1.1) smokers compared to women married to nonsmokers. These findings were largely interpreted as refuting the earlier studies, particularly since the author concluded that "nonsmokers married to smoking husbands showed very little, if any, increased risk of lung cancer." However, the RR estimates were above 1.0 and the 95% confidence limits associated with husband's smoking were large enough (0.9–1.9 for light smokers; 0.8–1.6 for heavy smokers) to accommodate a small to moderate effect of passive smoking.

TABLE 2.—*RRs of lung cancer other than adenocarcinoma among nonsmoking Greek women according to the smoking habits of their husbands*[a]

Husband's smoking status	Cases	Controls	RR	95% CI
Nonsmoker	24	109	1.0	—
Ex-smoker	15	35	1.9	0.9–4.1
1–20 cigarettes/day	24	56	1.9	1.0–3.7
≥21 cigarettes/day	14	25	2.5	0.9–7.0

[a] Data from (*5, 6*).

Other Studies in the United States

Six case-control studies that estimated lung cancer risks for passive smoking among nonsmokers have recently been completed in different areas of the United States. Most had relatively small numbers of cases, since the great majority of lung cancers in this country occur among smokers. They also tended to focus on women, as there were even fewer nonsmoking men with lung cancer available for investigation.

In a hospital-based investigation into the elevated lung cancer mortality rates among Louisiana's southern parishes (*13*), only 10 male lung cancer patients (of a total of over 1,000) and 25 ever-married female cases (of 302) had never smoked cigarettes. After 4 cases were excluded because of inadequate information on spouse's smoking habits, a twofold increased risk of lung cancer was found for both male and female nonsmokers whose spouses smoked compared to those whose spouses did not smoke. The excess was threefold for those whose spouses smoked more than 2 packs per day. Some increase in risk was also noted among male smokers whose mothers had smoked, but no association was found for paternal smoking.

TABLE 3.—*RRs of lung cancer among nonsmoking women married to smokers reported from epidemiologic studies in the United States*

Study,[a] author (reference)	Spouse smoked	Cases	Controls	RR	95% CI
Garfinkel (*12*)	No	65	—[a]	1.2	0.8–1.6
	Yes	88			
Correa et al. (*13*)	No	8	72	2.1	0.8–5.5
	Yes	14	61		
Kabat and Wynder (*15*)	No	11	10	0.8	0.3–2.5
	Yes	13	15		
Wu et al. (*16*)	No	9	19	1.2	0.6–2.5
	Yes	19	33		
Garfinkel et al. (*18*)	No	43	148	1.2	0.9–1.6
	Yes	91	254		

[a] All investigations were case-control studies, except the first, which was a cohort study ascertaining lung cancer deaths over a 6-yr period among 176,000 women.

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TABLE 4.—*RRs of lung cancer among nonsmoking women married to smokers reported from case-control studies in other countries*

Study, author (reference)	Country	Spouse smoked	Cases	Controls	RR	95% CI
Akiba et al. (*20*)	Japan	No	21	82	1.5	0.9-2.6
		Yes	73	188		
Chan et al. (*21*)	Hong Kong	No	50	73	0.8	0.4-1.3
		Yes	34	66		
Koo et al. (*23*)	Hong Kong	No	35	70	1.5	0.9-2.7
		Yes	51	66		
Lee et al. (*25*)	Great Britain	No	5	16	1.6	0.5-5.0
		Yes	19	38		
Pershagen et al. (*26*)	Sweden	—[a]	67	134	1.2	0.6-2.1

[a] Data in (*26*) not presented separately by smoking status of spouse.

Dalager et al. (*14*) subsequently added data on 14 male cases from a case-control study in New Jersey to the Louisiana data and noted that the trend toward increasing risk associated with number of cigarettes smoked per day by the spouse was stronger for squamous cell carcinoma than for adenocarcinoma of the lung. When information from a case-control study of lung cancer in Texas was included, the total number of cases who had never used tobacco products was raised to 99. The only exposure variable available for all these subjects was duration of living with a household member (parent, spouse, or other individual) who smoked. There was no increase in risk (RR=0.8; 95% CI=0.5-1.3) associated with ever living with a smoker, but a slight increase (RR=1.2; 95% CI=0.6-2.5) was found when the duration of exposure exceeded 40 years.

In a multicenter case-control study, Kabat and Wynder (*15*) reported that among 36 nonsmoking male and female lung cancer patients, the proportion of smoking spouses was not higher than expected (RR=0.9; 95% CI=0.3-2.1). The authors did not present risk estimates according to the number of cigarettes smoked by the spouse. Among nonsmoking males, an increased risk of lung cancer (RR=3.3; 95% CI=1.0-10.5) was reported for those exposed to tobacco smoke at work.

Wu et al. (*16*) noted 20 and 30% increases in the risk of adenocarcinoma of the lung among nonsmoking women in Los Angeles who were exposed to passive smoking from spouses or at work, respectively. Interviewed were 29 nonsmoking patients and 62 nonsmoking controls. Only 2 nonsmoking patients had squamous cell cancers, precluding evaluation of risks for this type of lung cancer. Combining years exposed at home or at work, the increase in risk of lung adenocarcinoma rose to twofold for those in the highest duration of exposure category, although the trend was not statistically significant. No increase in adenocarcinoma among nonsmokers was associated with exposure to parental tobacco smoking during childhood, but having a mother or father who smoked yielded RR estimates of 1.7 and 1.5, respectively, among the total group, most of whom were smokers.

In a hospital-based case-control investigation in North Carolina (*17*) designed to explore the effect of passive smoking on many cancers, 22 patients had lung cancer. There was a 50% increase in risk (95% CI=0.6-4.3) of this tumor among persons married to smokers. All but 2 of the lung cancer patients were smokers themselves, however, limiting the study's ability to assess an association with passive smoking.

Garfinkel et al. (*18*) carried out the largest case-control study assessing passive smoking to date. In a hospital-based investigation in New Jersey and Ohio, nonsmoking women with lung cancer (134 cases) were matched to nonsmoking women with colorectal cancer (402 controls). Information was sought from the subjects, or more often their next of kin, not only on spouse's smoking habits, but also on exposures to passive smoking outside the home. There was no evidence of a trend of increasing risk of lung cancer with increasing hours per day of exposure to passive smoking. More cases than controls, however, were found to have husbands who had smoked. The overall excess was 20% (RR=1.2; 95% CI=1.0-1.7) and increased to 100% (RR=2.0; 95% CI=1.1-3.5) among those whose husbands smoked 2 or more packs of cigarettes per day. The RR estimates tended to be slightly higher when husband's smoking was categorized according to cigarettes smoked at home. This study is unusual in that the hospital control group consisted of admissions for a single disease entity rather than a variety of conditions. Hence case-control differences might reflect unusual characteristics of colorectal cancer as opposed to lung cancer. Colorectal cancer is unrelated to smoking habits (*19*) and presumably to passive smoking, so the controls used should be appropriate.

Studies in Other Countries

Several recent publications have evaluated the relation of passive smoking to lung cancer in other countries, mainly through case-control studies (table 4). Utilizing data from a case-control study of lung cancer among a cohort of atomic bomb survivors in Hiroshima and Nagasaki, Akiba et al. (*20*) found a 50% increase in the risk of lung cancer among nonsmoking women whose husbands smoked. There was a progressive increase in risk with amount smoked by the husband, the excess reaching twofold for women married to men who smoked 30 or more cigarettes per day. A reduction in lung cancer risk was also reported following cessation of exposure to husband's smoking. The findings, based on 94 nonsmoking cases and 270 nonsmoking controls, are

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quantitatively very similar to those reported in the Hirayama cohort study (*3, 4*), despite different populations covered and different methods employed. Most of the interviews were with the next of kin of deceased cases and controls, but the information on smoking habits closely resembled that obtained from the women themselves during routine surveys of atomic bomb survivors in the 1960's. This comparison provided independent confirmation by the relative of the nonsmoking status of most of the women, both cases and controls, arguing against the possibility that Japanese women tend to report themselves as nonsmokers when they actually smoke.

In Hong Kong, where the rates of lung cancer among females are high by world standards, two investigations provided mixed results. Chan et al. (*21, 22*) reported that 41% of nonsmoking female cases versus 48% of orthopedic controls were passive smokers, although the criteria used to define exposure are not clear. Seeking information on lifetime exposure to environmental tobacco smoke in the home and workplace, Koo et al. (*23*) interviewed 88 nonsmoking women with lung cancer and 137 nonsmoking neighborhood-matched controls. The RR of lung cancer among women married to husbands who smoked in their presence was 1.5 (95% CI=0.9-2.7), rising slightly among those who were exposed to environmental tobacco smoke either at home or at work compared to those not exposed at either setting (Koo LC: Personal communication). There was no increasing trend with amount smoked, however, and the total number of hours of exposure per year from all sources of passive smoking was somewhat less for the cases than controls. When risk estimates were calculated according to cell type, an increase in risk associated with passive smoking was more apparent for squamous cell cancer than adenocarcinoma of the lung.

Limited information on this issue is available from western Europe. A case series of 39 female nonsmoking lung cancer patients in the Federal Republic of Germany was described by Knoth et al. (*24*). About 60% were reported to live with smokers. No control group was used, but the authors referred to census statistics indicating that only 22% of males aged 50-69 were smokers. The appropriateness of this comparison is doubtful, because of likely differences in the definition of smoking status (e.g., the census ascertained current smoking prevalence at a fixed point in time, whereas apparently no such time restriction was placed on the cases) and because some of the patients may have lived with more than a single individual.

As part of a hospital-based case-control study in Great Britain, Lee et al. (*25*) interviewed 47 married lung cancer patients and 96 controls admitted for conditions unrelated to smoking, who had never smoked. Information on spouse's smoking habits was sought from the study subjects and the spouses themselves. The RR of lung cancer among nonsmoking women married to smokers was 1.6 (95% CI=0.4-5.6) when smoking habits during marriage were reported by the husbands and 1.0 (95% CI=0.2-4.4) among nonsmoking men whose wives reported themselves as smokers. The RRs were lower for women and higher for men when data from the subjects but not the spouses were used.

Among 2 cohorts of nonsmoking Swedish women, incident cases of lung cancer plus controls were identified during 1963-80 (*26*). Questionnaires completed in 1984 on 67 patients or their next of kin and about four times as many age-matched controls provided information on the spouse's smoking habits. There was little overall increased risk of lung cancer among women married to smokers, but a 2.5-fold excess (95% CI= 1.0-6.7) was found for Kreyberg I lung cancer, predominantly squamous and oat cell carcinomas. For both Kreyberg type I and II lung cancers, risks were most elevated for the heavy-exposure group, namely, those married to men who smoked more than 15 cigarettes per day during 30 or more years of marriage.

Only limited information is available from cohort studies conducted since the observations of Hirayama (*1*) and Garfinkel (*12*). In a follow-up survey in Scotland, Gillis et al. (*27*) noted excess lung cancer mortality among nonsmoking males but not females exposed to passive smoking, but the numbers involved were quite small (6 male and 8 female lung cancer deaths).

SUMMARY RR ESTIMATES

We combined results from the epidemiologic studies listed in tables 3 and 4 with those of Hirayama (*3*) and Trichopoulos et al. (*5, 6*), weighting the RRs from each study according to the Mantel-Haenszel procedure (*28*). **Based on the overall data, the summary RR estimate of lung cancer among nonsmoking women whose husbands smoked was 1.3 (95% CI=1.1-1.5).**

As reported in several investigations evaluating dose-response trends, the RR estimates tend to be higher for women married to heavy smokers (table 5). Although the definition of a heavy smoker varied across the studies, if results for the high exposure categories are combined, the summary RR estimate of lung cancer associated with heavy passive smoking is 1.7 (95% CI=1.4-2.1).

TABLE 5.—*RRs of lung cancer among nonsmoking women, according to number of cigarettes smoked per day by their husbands, reported from epidemiologic studies in the United States and other countries*

Study, author (reference)	Husband's smoking status		
	Nonsmoker	Light	Heavy*
Garfinkel (*12*)	1.0	1.3	1.1
Correa et al. (*13*)	1.0	1.2	3.5
Wu et al. (*16*)	1.0	1.2	2.0
Garfinkel et al. (*18*)	1.0	1.1	2.0
Akiba et al. (*20*)	1.0	1.4	2.1
Koo et al. (*23*)	1.0	1.9	1.2
Pershagen et al. (*26*)	1.0	1.0	3.2

* Heavy smokers are defined as those who smoked ≥20 cigarettes per day in (*12*) and (*25*); ≥30 cigarettes per day in (*20*); ≥40 cigarettes per day in (*13*) and (*18*); ≥15 cigarettes per day among those married at least 30 yr in (*26*); and as those with ≥30 yr of passive smoking exposure in (*16*).

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The cumulative epidemiologic evidence to date thus suggests that nonsmokers married to smokers experience a small to moderate increased risk of lung cancer. There is uncertainty, however, about the causal nature of the association, especially in view of limitations in assessing exposure to environmental tobacco smoke.

EXPOSURE ASSESSMENT

While women married to smokers tend to receive greater exposure to ambient smoke than women married to nonsmokers, it is apparent that husband's smoking status is an imperfect correlate of total exposure to environmental tobacco smoke. Such was suggested by a survey of 35,000 nonsmoking male and female participants of a health maintenance organization in San Francisco and Oakland who answered questions regarding their hours of exposure to environmental tobacco smoke at home, in office rooms and other confined spaces, or in larger areas outside the home (*29*). It was found that nearly one-half of the female nonsmokers married to smokers reported no exposure to passive smoking in the home, while about one-third of the women married to nonsmokers reported some passive smoking outside the home. Although the survey focused on current exposures and included many young adults, whose practices are not necessarily those of women in the 55-70 age range where lung cancer usually arises, it appears that information on husband's smoking habits yields only an approximate measure of environmental tobacco smoke within the home and a crude indication of total exposure. **The survey did reveal, however, that even today the spouse is the dominant source of passive smoking exposure among nonsmokers who are married to smokers.**

Although interviews have been the method of ascertaining exposure to ambient tobacco smoke, there is mounting interest in supplementing self-reported information with more objective measures based on laboratory assessment of tobacco smoke aerosols and biological specimens obtained from nonsmokers. Biochemical assessment of passive smoking is complicated by the presence of over 3,000 substances that have been detected in tobacco and its combustion products, including a great number and variety of carcinogens, cocarcinogens, promoting agents, and mutagens (*19, 30*), many of which tend to vary in concentration between mainstream and sidestream smoke. Mainstream smoke arises during puffs and passes through the butt end of the cigarette, whereas sidestream smoke is generated by the passive burning of the cigarette and is emitted directly into the air. Since about 80% of the tobacco is usually burned between puffs, indoor pollution from environmental tobacco smoke comes mainly from sidestream smoke, with exhaled mainstream smoke making the smaller contribution (*31*). Table 6 lists some of the constituents that have been found in the air of smoke-filled rooms in homes, offices, restaurants, and bars and provides ratios of the levels of the substances in sidestream versus mainstream cigarette smoke determined under experimental conditions. As indicated in the table, some components such as the nitrosamines and various particulates occur in much greater concentrations in sidestream smoke. In addition, sidestream smoke may increase exposure to other respiratory carcinogens, including radon and its daughter products (*32*). In Sweden radon levels in the households of smokers were more than double those of nonsmokers, possibly because ambient tobacco smoke increases the number of particulates to which radon products can cling.

TABLE 6.—*Selected constituents of tobacco smoke and their approximate ratio in sidestream to mainstream smoke*[a]

Constituent	Ratio in sidestream to mainstream smoke
Nitrosamines	5-437
Ammonia	73-150
Formaldehyde	50
2-Naphthylamine	39
Aniline	30
Nickel	0.2-31
Acrolein	12
Carbon dioxide	8
Cadmium	4-7
Carbon monoxide	2-5
Methane	3
Nicotine	2-3
Benzo[α]pyrene	2-3
Phenol	3
Tar	1-2
Acetylene	0.8
Hydrogen cyanide	0.05-0.4

[a] Adapted from (*19, 30, 31, 53*).

Although cigarette smokers obviously inhale considerably greater amounts of tobacco smoke than can be achieved by involuntary inhalation of smoke, the exposures to particular agents from passive versus active smoking have not been fully characterized (*33*). Some comparative estimates have been made, however. One, based on experimentally determined air measurements, estimated that airborne levels of aldehyde, total particulate matter, and nicotine inhaled by passive smoking in 1 hour would be, respectively, about 1/4, 1/11, and 1/50 the levels inhaled by smoking 1 cigarette (*34*). On the other hand, the amount of volatile nitrosamines inhaled by a passive smoker in 1 hour in a closed environment, such as a commuter train bar, was reported as equivalent to that received by smoking over one-half pack of filter cigarettes (*35*). Repace and Lowrey (*36*) estimated a range of 0-14 mg tar/day (average, 1.4 mg) received by nonsmokers, corresponding to the tar obtained from smoking about 0.1-1 cigarette. Contributing to the difficulty of assessing exposure to lung tissue are different routes of exposure, with passive smokers generally inhaling through nasal passages, as opposed to the mouth and throat among direct smokers. Little is known about the deposition of tobacco smoke aerosols within the bronchus and lung, although deposition fractions have been reported to be less for sidestream than mainstream smoke (*37*). Somewhat smaller particle sizes have been measured for sidestream smoke (*31*), suggest-

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ing that a greater proportion of the exposure from passive smoking reaches the more distal portions of the lungs.

The biochemical assessments perhaps most relevant to environmental tobacco smoke exposure have involved assays of smoke constituents or their metabolites in body fluids. Saliva, blood, and urine specimens have been collected from passive smokers for determinations of several substances, including nicotine and cotinine, the major metabolite of nicotine. Hoffmann et al. (*38*) exposed 10 nonsmoking volunteers for 80 minutes in an experimentally controlled room to steady-state pollution from 4 standard cigarettes and almost immediately observed sharp rises in salivary nicotine, with subsequent tripling of salivary, plasma, and urinary cotinine levels, but little change in thiocyanate or carboxyhemoglobin. Elevated cotinine levels among passive smokers have been a consistent finding in other experimental studies, as well as in naturally occurring settings (*39*). Wald et al. (*40*) noted a tenfold gradient in urinary cotinine among 199 nonsmokers, with levels rising in proportion to duration of exposure to environmental tobacco smoke in the week prior to urine collection. Similar trends have been observed in other surveys of nonsmoking adults in Great Britain and Japan (*41, 42*) and in a population-based sampling of 569 British school children (*43*). Mean urinary cotinine concentrations among North Carolina infants living with smokers were over 20 times higher than the corresponding levels among infants whose parents did not smoke (*44*). The levels also tended to increase with the number of cigarettes the mother smoked in the preceding 24 hours.

These studies leave little doubt that nonsmokers actually inhale and metabolize sidestream smoke constituents. The levels of most substances, such as cotinine, in passive smokers appear to be much less than in smokers themselves. The cotinine concentrations among passive smokers are generally about 1/100 or less those of direct smokers, although the fraction is much higher in Japan (*42*). In the two surveys of adults comparing "heavy" passive to active smoking, the fractions were 1/50 in Great Britain (*40*) and 1/7 in Japan (*42*). Translating these figures into cigarette equivalents suggests that nonsmokers heavily exposed to environmental tobacco smoke receive nicotine in amounts similar to those obtained by smoking between 1/2 and 3 cigarettes per day. The lower level probably reflects the situation in the United States, while the higher fraction in Japan may be influenced by greater degrees of crowding and smaller average room sizes. Hence, if involuntary smoking exposures to nicotine approximate those to the carcinogens in tobacco smoke, then the risks of lung cancer associated with passive smoking might be estimated by assuming that heavy passive smoking is equivalent to smoking about 1 cigarette every other day. This may be an underestimate, however, since ingredients in tobacco smoke other than nicotine appear responsible for smoking-induced lung cancer, and passive smokers inhale comparatively less nicotine than several other substances, including nitrosamines. Thus passive smoking might result in exposures to specific carcinogens in ambient tobacco smoke equivalent to smoking up to a few cigarettes per day.

Precise estimates of the risk of lung cancer associated with smoking 1 or 2 cigarettes per day are not available, since not many smoke so few cigarettes daily. However, three major prospective cohort studies of mortality among smokers [the American Cancer Society's investigation of nearly 500,000 men (*45*); the 16-yr follow-up of 250,000 U.S. veterans (*46*); and the 20-yr follow-up of 34,000 British doctors (*47*)] revealed RRs of lung cancer of 4.6, 4.8, and 7.8 among smokers of 1–9, 1–9, and 1–14 cigarettes per day, respectively. Linear interpolation between these values and the base-line level of 1.0 for nonsmokers would yield estimated RRs for smokers of a few cigarettes per day of 1.5-fold to twofold, the same order of increase associated with high levels of passive smoking.

EVALUATING CAUSAL SIGNIFICANCE

The evidence from epidemiologic investigations suggests that nonsmoking women married to smokers have experienced an increase in lung cancer risk. Our calculations summarizing the available data place the excess at about 30%. Since environmental tobacco smoke contains many agents that may contribute to pulmonary carcinogenesis and since constituents of tobacco smoke have been detected in body fluids of passive smokers, it is biologically plausible that a causal relation exists between passive smoking and lung cancer. This interpretation is enhanced by the replication of findings in different populations around the world, by a dose-response effect with excess risks of about 70% among nonsmokers heavily exposed to ambient tobacco smoke, by cell type predilections resembling those associated with direct smoking, and by the similarity in risk estimates between heavy passive smokers and exceptionally light active smokers.

The current evidence, however, must still be interpreted with caution. It has been difficult to quantify actual exposure to environmental tobacco smoke, and estimates based on smoking habits of spouses are relatively crude approximations. There is also concern that women married to smokers differ from women married to nonsmokers in ways that influence lung cancer risk. In the passive smoking survey of San Francisco and Oakland (*29*), the reported passive smoking exposures from all sources were higher for whites, the young, those without a college education, heavy drinkers of alcoholic beverages, and workers exposed to hazardous substances. Race, age, and education were usually controlled for in the design or analysis of the studies reviewed, however, and alcohol is not generally recognized as an independent risk factor for lung cancer (*48*). Occupational exposure to respiratory carcinogens (*49*) may occur among women married to smokers, but the numbers would be very small and not likely to confound the relationships observed. There is evidence that intake of foods high in beta-carotene and other nutrients may lower the risk of lung cancer (*50*). It is not known

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whether women married to smokers consume less of these foods, but adjustment for intake of green vegetables and other vitamin A-containing foods in two studies of passive smoking (*3*, *14*) had little effect on the estimates of lung cancer risk.

More extensive and innovative studies are needed to evaluate and clarify the causal nature of the relation between lung cancer and passive smoking. Although attention will probably continue to center on nonsmoking women married to smokers, the group most likely to provide the largest amount of relevant data, special efforts should be made to quantify more precisely the exposure levels to ambient tobacco smoke both within and outside the home. Larger studies will be required to assess fully the small increases in RR expected from passive smoking, confirm trends of greater risk with higher levels of exposure, adequately adjust for confounding factors, and search for interactions with host susceptibility (e.g., genetic or nutritional measures). The impact of transplacental and early life exposures to parental smoking should also be investigated as a risk factor that might, as suggested by animal models, potentiate the effects of later exposure to tobacco smoke or other carcinogenic hazards (*13*). The tendency for lung cancer to aggregate in families (*51*) should be investigated to identify the possible role of passive smoking as well as genetic susceptibility. In addition, there is potential for other long-term consequences such as coronary artery disease (*52*), indicating the importance of further research to clarify the role of passive smoking on the risk of various chronic diseases. Whenever possible, epidemiologic evaluation of passive smoking should incorporate laboratory measures of tobacco smoke components and their by-products, plus indicators of biologic response and interactions.

CONCLUSION

Further research is needed to evaluate the etiologic role of passive smoking; however, **it would seem prudent to regard the existing evidence as highly suggestive that long-term exposure to environmental tobacco smoke increases the risk of lung cancer.**

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